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(54) Title: GLUCOSE SENSOR SYSTEM

(57) Abstract: A sensor (10) for detection of an analyte, such as glucose, in a fluid, such as blood or other body fluid, is formed by printing components of the sensor, such as electrodes (24, 26, 28), and a sensing element (18), which contains an oxidorectase enzyme, such as glucose oxidase, on a suitable support (12). In one embodiment, the support comprises the wall (100) of a catheter (102), which is inserted into a patient's body.

GLUCOSE SENSOR SYSTEM

Background of the Invention

The present invention relates to the sensor arts. It finds particular application in conjunction with printed electrochemical sensors of the type used, for example, in the subcutaneous or transcutaneous monitoring of blood glucose levels in a diabetic person, and will be described with particular reference thereto. It should be appreciated, however, that the invention is also applicable to the determination of other electrochemically detectable substances present in body fluids and non-body fluids.

The regulation of blood sugar levels in diabetics by careful dosage of insulin has been studied extensively. To ensure that the diabetic receives a correct dosage of insulin, it is particularly important to monitor the diabetic's glucose level. Thin film electrochemical sensors are generally known in the art for use in a variety of specialized applications, including the detection of glucose. Thick film sensors are also known. Such thin or thick film sensors may comprise one or more thin conductors applied by photolithography mask and etch techniques between thin layers of a nonconductive material, such as a polyimide film. Silk screen printing techniques have also been used in the preparation of sensors. The conductors are shaped to define distal end sensor tips having an appropriate electrode material thereon, in combination with proximal end contact pads adapted for conductive connection with appropriate electronic monitoring equipment. In recent years, thin film sensors of this type have been proposed for

use as a transcutaneous sensor in medical applications. As one example, thin film sensors have been designed for monitoring blood glucose levels in a diabetic person, with the distal end sensor electrode s positioned subcutaneously in direct contact with the person's blood stream.

Such mask and etching techniques are time consuming and costly. Because body fluids tend to degrade the electrode materials and proteins tend to deposit on the electrodes, the sensors have a relatively short life. For diabetics and others who monitor glucose or other body chemicals frequently and for extended periods it is therefore desirable to have an inexpensive sensor which is disposable at intervals of a few days.

For measurement of glucose levels, sensors typically employ an oxidase enzyme, particularly glucose oxidase. The oxidase acts on a substrate or analyte, such as glucose, to produce hydrogen peroxide, and in the process, oxygen is consumed. The concentration of glucose can be determined indirectly, such as by detecting the depletion of oxygen or the generation of reaction products, such as hydrogen peroxide or gluconic acid. U.S. Patent No. 4,970,145 discloses electrodes formed from platinized carbon particles on which an enzyme, such as glucose oxidase, is immobilized. U.S. Patent No. 5,160,416 discloses similar electrodes in which a mixture of the enzyme with finely divided platinum group metal or oxide particles and carbon powder in a suitable binder is deposited on an electrically conductive support material, such as carbon paper or a platinum strip. Both patents disclose the use of amperometric techniques to determine glucose levels.

The present invention provides a new and improved sensor and method of use which overcomes the above-referenced problems and others.

Summary of the Invention

A sensor system formed by printing electrodes on a support has a variety of applications for the detection of glucose and other chemicals in vivo and in vitro.

One advantage of the present invention is that a disposable sensor is readily formed.

Another advantage is that the sensor may be formed on a wall of a catheter.

Still further advantages of the present invention will become apparent to those of ordinary skill in the art upon reading and understanding the following detailed description of the preferred embodiments.

Brief Description of the Drawings

The invention may take form in various components and arrangements of components, and in various steps and arrangements of steps. The drawings are only for purposes of illustrating a preferred embodiment and are not to be construed as limiting the invention.

FIGURE 1 is a top view of a sensor according to the present invention;

FIGURE 2 is a perspective sectional view in partial section through A-A of the sensor of FIGURE 1;

FIGURE 3 is a schematic view of a combination infusion pump and glucose meter according to the present invention;

FIGURE 4 is a schematic sectional view of a sensor inserted through the wall of a catheter;

FIGURE 5 shows a sensor in use in a closed loop system;

FIGURE 6 is a schematic sectional view of a subcutaneous sensor system mounted to an exterior of a catheter wall and signaling a glucose meter, according to the present invention;

FIGURE 7 is a schematic sectional view of a subcutaneous sensor mounted to an interior of a catheter

wall and signaling a glucose meter coupled to an insulin pump;

FIGURE 8 is a top view of a sheet of support material with sensors printed thereon;

FIGURE 9 is a side perspective view of the support sheet of FIGURE 8 rolled into a catheter shape with the sensors on the exterior; and

FIGURE 10 is a side sectional view of an infusion set with a catheter passing through a person's skin.

Detailed Description of the Preferred Embodiments

With reference to FIGURES 1 and 2, a sensor **10** is shown. While the sensor is described with reference to glucose detection, it will be appreciated that the sensor may also be used for detection of other electrochemically detectable chemicals.

The sensor comprises a support **12**, formed from an insulative material, such as a sheet of polyester, polycarbonate, or polyimide. The support defines a well **14** adjacent one end of its upper surface **16**. A sensing material **18** is deposited at the base and on the sides of the well. The sensing material **18** includes an oxidoreductase enzyme, such as glucose oxidase, with is capable of catalyzing the reaction of a substrate or analyte (e.g., glucose). In the case of glucose, the glucose oxidase enzyme acts on the glucose to produce hydrogen peroxide, the reaction consuming oxygen. Other suitable oxidoreductases include uricase, lactase oxidase, cholesterol oxidase, and other peroxide-producing enzymes. Combinations of enzymes may also be used, as well as combinations of non-oxidases and oxidases, the non-oxidase acting on a substrate of interest to produce an oxidizable substrate for the oxidase. One such combination is beta-galactosidase and glucose oxidase for the determination of lactose.

The sensing material **18** preferably also includes a platinum group metal or metal oxide in finely divided form, which is relatively homogeneously mixed with the

oxidase. Suitable platinum group metals and oxides thereof include platinum, ruthenium, rhodium, iridium, palladium, and their oxides, and combinations thereof. Ruthenium is a particularly preferred metal. The sensing material may further include a carbon-containing material, such as finely divided carbon or graphite powder. Such materials preferably have a relatively large surface area of about 10 m^3/gm or higher, most preferably, in the range of 200-600 m^3/g. Preferably, the platinum group metal or metal oxide has a particle size in the range of from about 1 nm to about 20 μm, most preferably, in the range of 1-4 μm.

A droplet or layer of an analyte-containing liquid or viscous fluid **20** to be analyzed for the substrate is added to the well. An electrode system **22** detects a product generated (e.g., hydrogen peroxide or gluconic acid) or a chemical consumed (e.g., oxygen). Hydrogen peroxide is a particularly preferred detectable substance. A variety of electrode systems may be employed for detection. FIGURES 1 and 2 show a 3-electrode system, with a working electrode **24**, reference electrode **26**, and a counter electrode **28**, laid down generally in parallel on the support surface so that at least a portion of each of the electrodes is in contact with the fluid **20**. However, other electrode systems may also be employed, such as a two electrode system employing working and reference electrodes.

The electrode system is in electrical contact with the analyte **20**. As shown in FIGURE 1, the electrodes take the form of strips, laid down on the support, with contact pads **30** at a proximal end of the support for electrically connecting the electrodes with electrochemical equipment (not shown). A variety of electrochemical measurement techniques may be employed with the electrode system, including amperometric and potentiometric techniques. For example, a voltage is periodically applied between the working and reference electrodes **24, 26** and the current generated due to reduction of hydrogen peroxide measured between the working and counter electrodes.

The electrode system generates an electrical signal (current in the above embodiment) which is related to (directly proportional to, in the case of glucose and hydrogen peroxide) the concentration of the analyte substance to be detected (e.g., glucose). Using a look-up table, the electrochemical monitoring system compares the detected signal with calibrated concentration/signal data and produces an output indicative of the concentration of glucose or other substance present.

Various conductive materials may be used for forming the electrodes. In a preferred embodiment, the working electrode is formed from nickel or silver, the counter electrode is carbon, and the reference electrode is an Ag/AgCl electrode. Other materials or combinations of materials may also be used as is known in the art.

The electrodes may be formed by a variety of techniques, including lithography, printing, and the like. The electrode materials, e.g., ruthenium and glucose oxidase for the sensing material **18**, are mixed together and combined with a carrier liquid to form a suspension which is deposited on the support. In a preferred embodiment, the electrodes **24**, **26**, **28**, and also the sensing material **18** and contact pads **30** are printed on the support material, for example by inkjet, offset, laser, silk-screen, or gravure printing techniques. Both thin and thick film printing techniques may be used.

Inks are prepared by combining the materials for the electrodes or sensing material with a suitable carrier, such as a liquid or a material which flows at the temperature of printing. The inks are then printed on the support and dried or otherwise fixed. The inks can be laid down in a multi-step process, by printing a first material, which is allowed to dry, followed by a second material, and so forth, until all the materials are laid down. In the case of the sensing material, the enzyme, metal or metal oxide, and carbon powder may be mixed together with a carrier liquid to form an ink which is printed on the

support. Or, the enzyme, metal or metal oxide, and carbon powder may be separately laid down, each one in a separate ink formulation.

For example, a thick film process can be used to produce the sensor. In this process, a silk screen printing process is preferably used. The design of the sensor elements is first transferred onto a screen (which can be a metal mesh or polymer screen) by a photographic method. The selected metal or conductive electrode materials can be prepared or purchased commercially in ink or paste form. Placing the substrate, such as a polyimide or other film, in a thick film printing printer with the patterned screening over the polyimide film, the ink or paste can be applied onto the polyimide surface through the patterned screen using a controlled squeegee. The ink can then be dried by heat or UV curing.

The carrier liquid may be an aqueous or organic liquid or combination thereof and is preferably one which is readily removed from the electrode material or sensing material after printing, e.g., by evaporation, although leave-in carriers are also contemplated. In the case of the sensing material, the enzyme is generally sensitive to heat. The ink is therefore dried or otherwise fixed at a temperature which does not adversely affect the activity of the enzyme.

Preferably, multiple sensors are printed at one time by forming an array of sensors on a large sheet of the support material. The sheet is then cut to form the individual sensors.

In one embodiment, the sensor **10** is used outside the body to determine the glucose level in a droplet of blood or other body fluid. The droplet is withdrawn from the body and placed in the well. To aid in positioning the droplet in the well, a layer **34** of a wicking material is attached to the support surface **16** over the general area of the well. The droplet is applied to the wicking material and carried thereby into the well.

To measure the glucose concentration, the sensor is electrically connected with an electrochemical monitoring system, such as a glucose meter **40** (See FIGURE 3). The glucose meter both supplies the applied voltage (or current) and detects the current (or voltage) signal generated. It will be appreciated that the two functions of applying voltage/current and detecting the signal generated may be performed by separate components, although for convenience these are shown as a single unit, the glucose meter.

FIGURE 3 shows the glucose meter in a housing **42**, which also holds an infusion pump **44**, although separate glucose meters are also contemplated. After applying the droplet, the sensor **10** is inserted into a suitably shaped slot **46** in the housing, the slot having electrical connectors (not shown) which electrically connect the contact pads **30** with the glucose meter. The glucose meter determines the glucose concentration and signals a controller **50** (which may be integral with or separate from the glucose meter). The controller **50** calculates an appropriate response to the detected level by accessing look-up tables. In one embodiment, the controller may recommend that a dose of a medicament (e.g., a number of ml of insulin) be supplied to the person (e.g., from the infusion pump). Or, the controller may recommend that the person ingest carbohydrate. The recommended dose or other action step to be taken is displayed in human readable form, such as on a display screen **54**. The person may accept the recommended dose, for example by pressing keys on a keypad **56**, or may enter a different dose to be taken. The controller then instructs the infusion pump **44** to deliver to the selected dose, for example, by operating a motor **58** to drive a piston **60** of a syringe **66** containing the medicament. The medicament, e.g., insulin, is carried by suitable tubing **68** from the syringe into the person's body.

In an alternate embodiment, the controller may override the person in selecting a suitable dose, so that the person is not injected with a dangerous level of the

medicament. In yet another embodiment, the personal input **56** is eliminated and the controller instructs the insulin pump directly.

In another embodiment, the sensor **10** is used to detect glucose or other body chemical a body fluid flowing through tubing, such as a catheter **70** (see FIGURE 4). For this embodiment, the support **12** is formed from a material (e.g., polyimide or polyurethane) and/or is shaped (e.g., with a rounded end **72** or pointed tip) so that it is capable of piercing the catheter wall **74**. In this embodiment, the sensor support **12** is preferably formed from a rigid material and of a sufficient thickness that does not readily break during piercing. Catheters, in general, are formed from a relatively soft material, which is capable of being pierced. The electrode system **22** is thereby positioned to be immersed in the body fluid or other liquid to be analyzed in the bore **76** of the catheter. In this embodiment, the well **14** and wicking membrane **34** may be eliminated as the electrodes **24,26,28** and sensor material **18** are in direct contact with the analyte. The wicking membrane may be replaced with a protein-impermeable membrane or coating **80** or other membrane which inhibits the passage of materials which may be detrimental to the operation of the sensor. The membrane covers those portions of the sensor which are affected by the detrimental materials, such as the electrodes and/or the sensing material. The membrane **80** is, however, permeable to at least glucose (or other chemical to be detected).

Suitable protein impermeable membranes may be formed from a mixture of 2-hydroxyethyl methacrylate (HEMA), N,N-dimethyl amino ethyl methacrylate (DMAEMA) and methacrylic acid (MA), although other protein-impermeable materials are also contemplated. Alternatively or additionally, a coating which resists blood coagulation and protein binding may also be used, such as a mixture of polyethylene glycol (PEG) and heparin.

With reference to FIGURE 5, the sensor of FIGURE 4 may be employed in a loop system, such as a dialysis

system (see FIGURE 5). The loop system has one fluid path defined by a first catheter 84 which carries body fluid, such as blood, from a patient's body 86 to a dialysis machine 88 or other suitable monitoring or treatment equipment. A second, return catheter 90, returns the treated body fluid back to the patient. The sensor 10 is inserted into one of the catheters 84, 90 (FIGURE 5 shows the sensor in the input line 84), to detect the glucose content of the fluid flowing therethrough. The sensor may be operated continuously or intermittently, every few minutes, or as appropriate, to monitor the changing glucose level. The sensor is electrically connected by wiring 92 (or radio telemetry) to a glucose meter 94, which may be housed with the dialysis machine. As before, the glucose meter uses electrochemical techniques to monitor glucose levels, for example, by directing the hydrogen peroxide generated by enzymatic conversion of the glucose in a small region of the body fluid adjacent the sensing element 18. When the glucose meter registers that the glucose level is within a predetermined range, the glucose meter instructs the dialysis machine 88 to cease purifying the blood or to take other appropriate action. Alternatively, this operation may be conducted by a trained operator, who reads the glucose level detected by the glucose meter and programs the dialysis machine accordingly.

In another embodiment, shown in FIGURE 6, the sensor is employed for subcutaneous monitoring of glucose concentrations. The sensor 10 is mounted to a wall 100 of a catheter tube 102 such as a cannula, which may be employed to deliver insulin, or other medicament, to the persons blood or subcutaneous fluid. An infusion set 104 connected with a suitable insulin pump similar to that illustrated in FIGURE 3, or other delivery apparatus, delivers insulin to the catheter, which carries the insulin through the skin 106 and into a blood vessel, e.g., an artery, or into the interstitial fluid. The sensor may be positioned on an exterior surface 108 of the canula wall 100, as shown in

FIGURE 6, or on an interior surface 110 of the wall, as shown in FIGURE 7. The sensor 10 generates an electrical signal in response to an applied voltage or current which is related to the glucose level in the blood vessel or interstitial fluid adjacent the sensor. Electrical wiring 112 (or radio telemetry) connects the sensor 10 with a glucose meter 114. As previously described, the glucose meter may be a separate unit (FIGURE 6) or housed together with an insulin pump 44 and controller 50 (see FIGURE 7), analogous to that shown in FIGURE 3.

When formed on the inside of the wall (FIGURE 7), the sensor 10 is used between dosages of insulin, when the catheter is filled primarily with interstitial fluid or blood and the fluid line 68 to the insulin pump 44 is preferably closed off.

The wiring 112 may be attached to the exterior 108 of the catheter wall 100 (FIGURE 6), attached to the interior surface 110, or integrally formed with the catheter wall 100 so that it is encased by the catheter wall (FIGURE 7).

In a preferred embodiment, illustrated in FIGURES 8 and 9, the electrodes 24, 26, 28 and sensing material 18 of the sensor 10, and optionally also a portion of the wiring 112 are applied directly to a surface 108, 110 of the catheter wall 100. The catheter wall 100 thus provides the support 12 for the sensor. The sensor may be formed, as shown in FIGURES 6 and 7, on an exterior or interior wall of the catheter, either by printing a preformed catheter or by forming the sensor components on a sheet 120 which is then rolled into the shape of the catheter and joined at a seam 122, either by welding or with a suitable adhesive.

The application of the sensor components 18, 24, 26, 28,30 is preferably achieved by printing the components on the sheet 120 or formed catheter, although other application methods are also contemplated. As shown in FIGURES 8 and 9, a number (two are shown) of sensors 10, 10' may be printed on a single catheter. As for the embodiment

of FIGURE 4, a protein impermeable membrane 80 is preferably formed over the sensor.

With reference now to FIGURE 10, the wiring 112 may be carried by the catheter 102 to a cannula housing 130 of the infusion set 104. The infusion set comprises the cannula housing, which holds the upstream end of the catheter 102, and an injection hub 132, which carries a needle 136. The injection hub is selectively linked to the cannula housing to supply insulin to the catheter via the needle 136. The needle is fluidly connected with the fluid line 68 and carries the medicament through a septum 138, mounted at the upstream end of the catheter, into the catheter bore.

The wiring 112 is connected to the glucose meter via a connection made when the hub 132 and cannula housing 130 are linked. Additional wiring 140 may be attached to the fluid line 68, in a similar manner to wiring 112, to electrically connect the wiring 112 with the glucose meter 114, or radio telemetry may be used to transfer the signal thereto.

To use the sensor *in vivo* (i.e., transcutaneously), the cannula 102 with the sensor 10 formed thereon is inserted into the person's body with an insertion needle (not shown), for example, by replacing the injection hub 132 of the infusion set 104 with an insertion hub having a needle which extends through the cannula to just beyond the distal end of the cannula. The needle is inserted through the skin, carrying the cannula with it.

Once the cannula has been inserted, the insertion needle is withdrawn and the insertion hub replaced with the injection hub. The sensor is then ready for use. The sensor may be used continuously or intermittently to provide glucose measurements over a period of hours or several days. Typically, diabetics change the site of insulin injection every few days to prevent damage to the skin. With each change of site a fresh catheter is inserted into the skin, accompanied by a fresh sensor 10 or sensors. The sensor is

preferably configured (for example, with a protein-impermeable membrane) so that the signal does not degrade appreciably within the period of use, preferably functioning effectively for several days, or more.

As will be readily appreciated, the catheter with the sensor **10** printed thereon need not be used with an infusion set **104** as shown in FIGURES 6 and 7, but may be used with other methods of drug delivery, or may be used with a blood treatment system, such as the dialysis unit of FIGURE 5.

With reference once more to FIGURES 1 and 2, the sensor **10** may also include a heating element **150**, such as a resistance heater, which is formed on the support **12** in a similar manner to the other components (such as by printing). The element may be formed from platinum or other suitable metal. Electrical current is supplied to the heating element **150** via leads **152, 154**, which are also printed on the support **12**. The heater is used to maintain the analyte at an appropriate temperature for measuring glucose concentration (i.e., by changes in H_2O_2 or O_2 concentration). Since the rate of the enzyme catalyzed reaction between glucose and oxygen is dependent on the temperature of the analyte fluid, it is preferable for the sensor to operate at a predetermined selected temperature. In this way, the glucose meter does not have to access a calibration table which corrects for fluctuations in temperature. The heater can also be used as a temperature detector, detecting the temperature of the adjacent fluid by measuring the voltage across the resistance heater at a determined applied current. As will be appreciated, the heater may be formed on an opposite surface of the support to that carrying the electrodes **24,26,28** and sensing element **18** (except where the catheter is used as the sensor support).

The sensor may also be configured to measure other properties of the analyte solution, such as pH. FIGURE 1 shows a pH detector **160** formed on the surface **16** of the

support 12 (e.g., by printing). Additionally or alternatively, the sensor may be adapted to measure ketones, which can build up to dangerous levels, particularly in the blood of diabetics.

While the sensor is particularly applicable to detecting glucose in blood and other body fluids of humans, it may also be used in other animals and for detection of glucose and other analytes in non-body fluids.

The invention has been described with reference to the preferred embodiment. Obviously, modifications and alterations will occur to others upon reading and understanding the preceding detailed description. It is intended that the invention be construed as including all such modifications and alterations insofar as they come within the scope of the appended claims or the equivalents thereof.

Having thus described the preferred embodiment, the invention is now claimed to be:

1. A method of detecting an analyte in solution, the method including:

providing a sensor (10) for detecting the analyte on a fluid line (102);

inserting the fluid line in a person's body;

detecting a concentration of the analyte in body fluid surrounding the fluid line.

2. The method of claim 1, wherein the analyte includes glucose.

3. The method of claim 1, further including:

communicating the sensed analyte to an analyte delivery system; and

delivering a medicament to the person through the fluid line in accordance with the concentration of the sensed analyte.

4. The method of claim 3, wherein the analyte includes glucose and the medicament includes insulin.

5. The method of claim 1, wherein the sensor includes electrodes and/or other sensing elements (24, 26, 28, 18) which are printed on to a surface of the fluid line.

6. The method of claim 5, wherein the step of printing includes printing a sheet of material with a plurality of electrodes and/or other sensing elements;

sectioning the sheet into strips, each strip having a set of electrodes and/or other sensing elements for the sensor; and

forming each of the strips into a fluid line.

7. The method of claim 6, wherein each of the strips is printed with electrodes or other sensing elements (24, 26, 28, 18) for sensing at least two properties of the body fluid.

8. The method of claim 7, wherein the at least two properties are selected from the group consisting of glucose concentration, ketone concentration, and pH.

9. A sensor for detecting glucose or other analyte in solution the sensor including at least one electrode which is printed on an exterior surface of a fluid line, the fluid line being for delivering a medicament to a person, the sensor being capable of detecting the glucose or other analyte in the person's body fluid adjacent the fluid line when the fluid line is inserted into the person's body.

10. The sensor of claim 9, wherein the sensor includes a sensing material (18) which includes an oxidoreductase enzyme.

11. The sensor of claim 10, wherein the sensing material further includes:

a platinum group metal or metal oxide in finely divided form.

12. The sensor of claim 11, wherein the platinum group metal or metal oxide is selected from the group consisting of platinum, ruthenium, rhodium, iridium, palladium, and their oxides, and combinations thereof.

13. A sensing and injection system comprising:

a source of a medicament;

a pump for delivering the medicament to a fluid line, the fluid line having an end capable of being inserted into a person's body;

a sensor for an analyte positioned at or adjacent the end of the fluid line such that the sensor is capable of detecting the concentration of the analyte in the person's body fluid adjacent the end of the fluid line when inserted; and

a means for receiving the detected analyte concentration and determining an amount of medicament to be supplied in response to the detected analyte concentration.

14. The system of claim 13, further including:

a means for controlling the pump to deliver the determined amount of medicament.

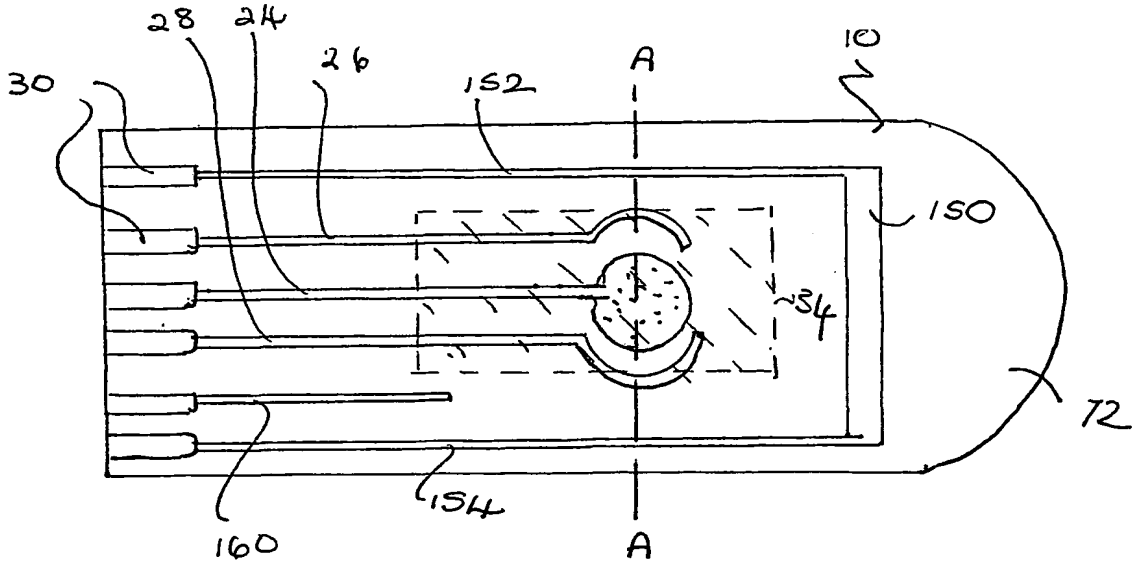

FIG. 1

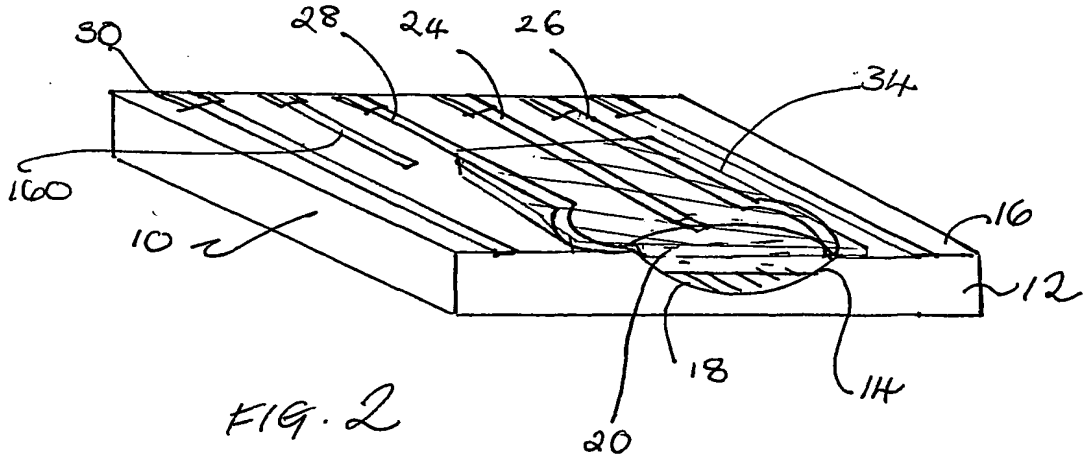

FIG. 2

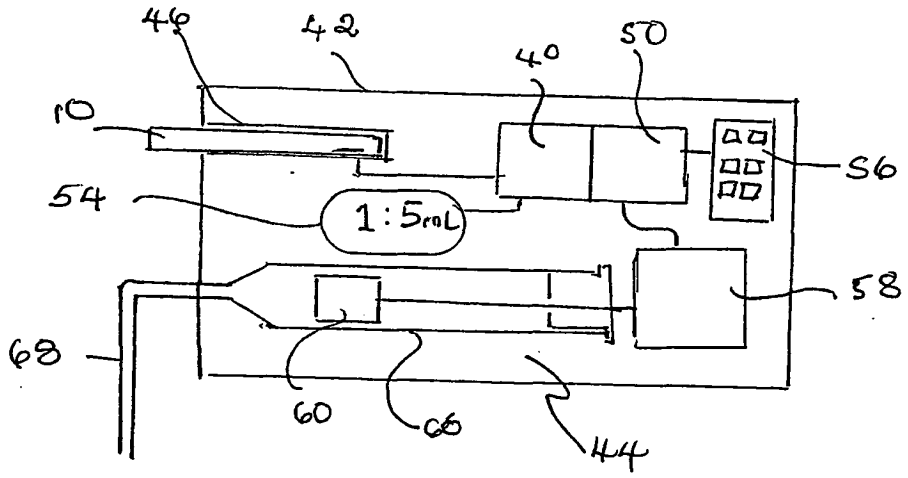

FIGURE 3

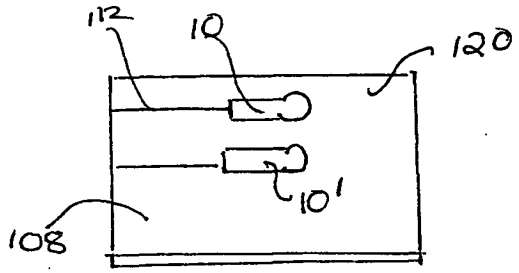

FIGURE 8

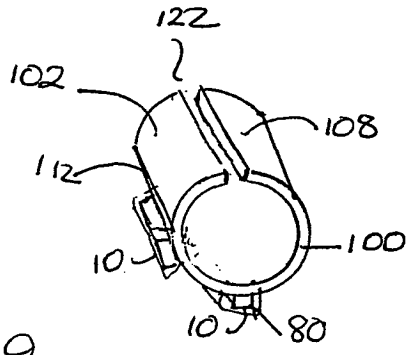

FIGURE 9

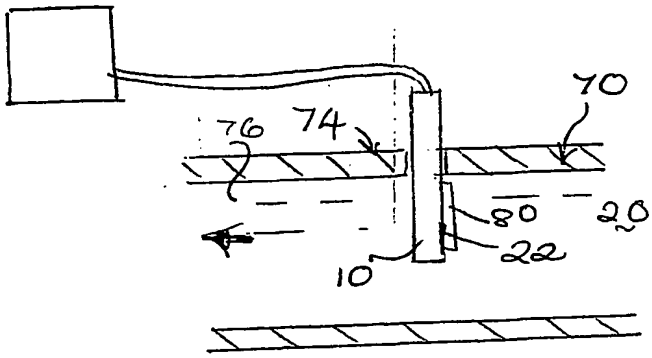

FIGURE 4

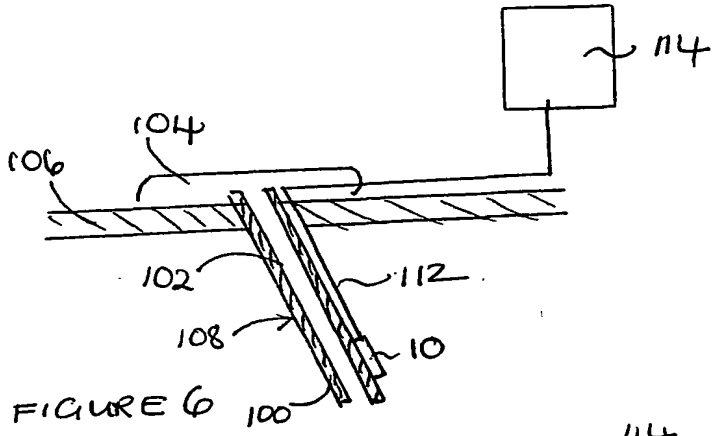

FIGURE 6

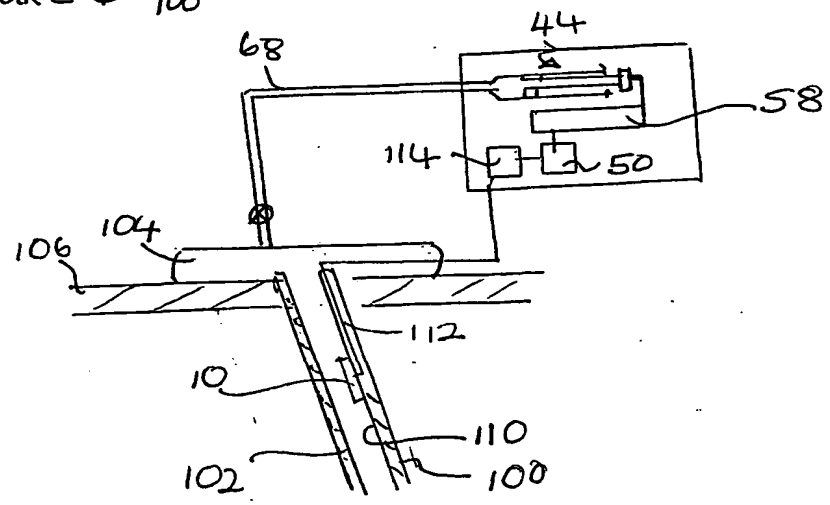

FIGURE 7

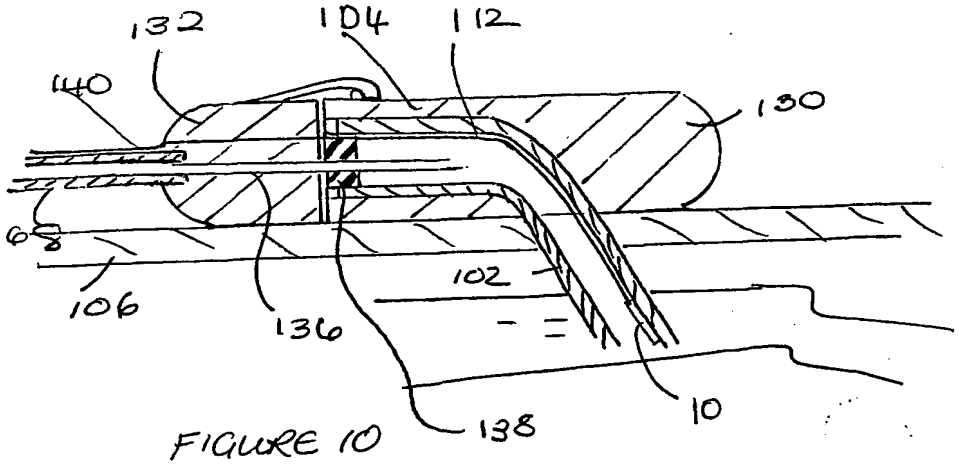

FIGURE 10

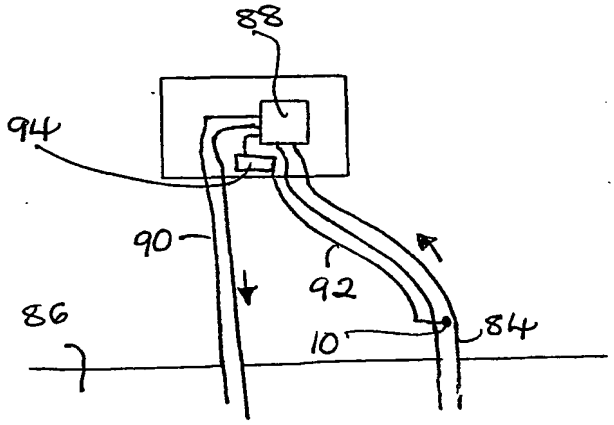

FIGURE 5

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(71) Applicant *(for all designated States except US)*: **NIPRO DIABETES SYSTEMS** [US/US]; 3150 N.W. 107 Avenue, Miami, FL 33172 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RAMEY, Kirk** [US/US]; 734 Blue Ridge Avenue, Bedford City, VA 24523 (US). **CHIUNG, Chiun, Liu** [CN/CN]; 2917 East Overlook Road, Cleveland, US 44118 (US).

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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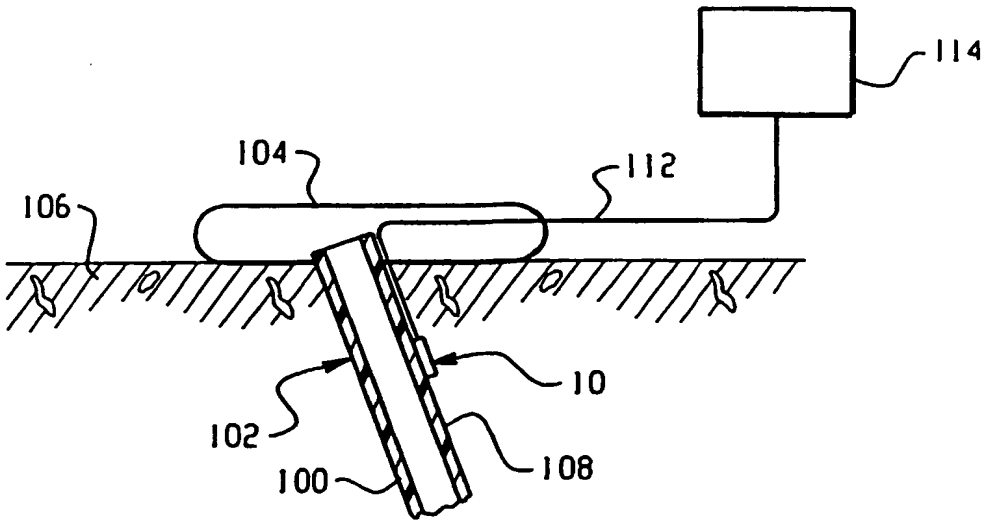
(54) Title: GLUCOSE SENSOR SYSTEM



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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 4 403 984 A (ASH STEPHEN R ET AL) 13 September 1983 (1983-09-13) column 14, line 43 -column 15, line 26 column 16, line 18 - line 45 figures 10,11,15,18	13,14 9-12
Y	US 5 497 772 A (LUCISANO JOSEPH Y ET AL) 12 March 1996 (1996-03-12) column 7, line 5 - line 11 column 8, line 14 -column 9, line 24	9-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 July 2002	06/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Martelli, L

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In tional application No.
PCT/US 01/51213

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-8
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...nation on patent family members

International Application No
PCT/US 01/51213

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4403984 A	13-09-1983	AU 6779481 A	22-07-1981
		DE 3050155 T0	15-04-1982
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		JP 56501714 T	26-11-1981
		SE 8105081 A	27-08-1981
		WO 8101794 A1	09-07-1981
US 5497772 A	12-03-1996	US 5660163 A	26-08-1997
		US 5791344 A	11-08-1998

Form PCT/ISA/210 (patent family annex) (July 1992)

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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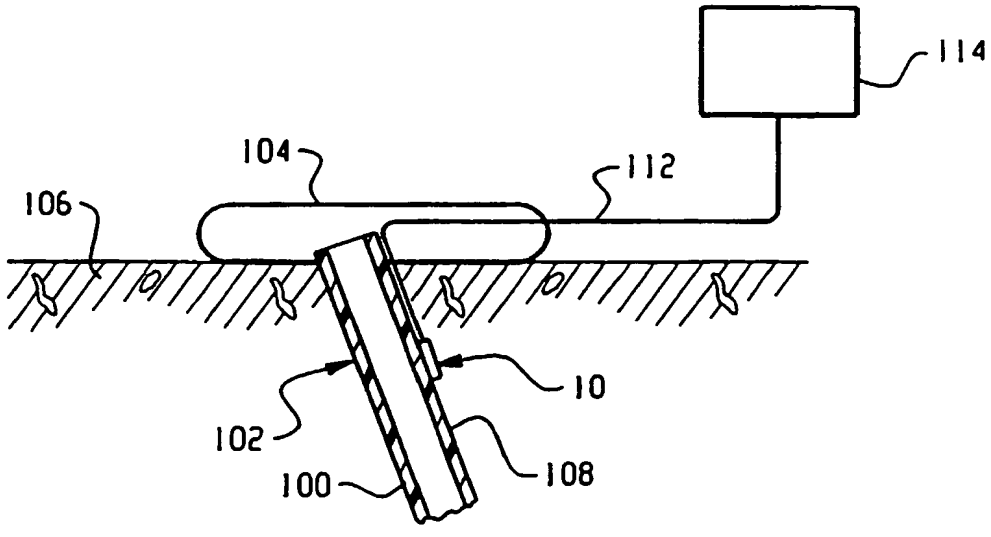
(54) Title: GLUCOSE SENSOR SYSTEM



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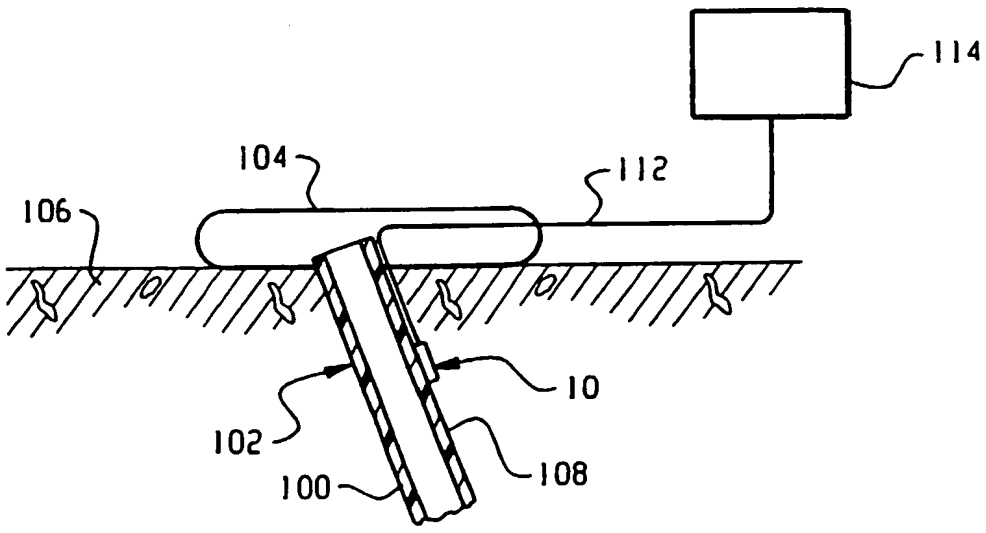
[Continued on next page]

(54) Title: GLUCOSE SENSOR SYSTEM



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GLUCOSE SENSOR SYSTEM

Background of the Invention

The present invention relates to the sensor arts. It finds particular application in conjunction with printed electrochemical sensors of the type used, for example, in the subcutaneous or transcutaneous monitoring of blood glucose levels in a diabetic person, and will be described with particular reference thereto. It should be appreciated, however, that the invention is also applicable to the determination of other electrochemically detectable substances present in body fluids and non-body fluids.

The regulation of blood sugar levels in diabetics by careful dosage of insulin has been studied extensively. To ensure that the diabetic receives a correct dosage of insulin, it is particularly important to monitor the diabetic's glucose level. Thin film electrochemical sensors are generally known in the art for use in a variety of specialized applications, including the detection of glucose. Thick film sensors are also known. Such thin or thick film sensors may comprise one or more thin conductors applied by photolithography mask and etch techniques between thin layers of a nonconductive material, such as a polyimide film. Silk screen printing techniques have also been used in the preparation of sensors. The conductors are shaped to define distal end sensor tips having an appropriate electrode material thereon, in combination with proximal end contact pads adapted for conductive connection with appropriate electronic monitoring equipment. In recent years, thin film sensors of this type have been proposed for

use as a transcutaneous sensor in medical applications. As one example, thin film sensors have been designed for monitoring blood glucose levels in a diabetic person, with the distal end sensor electrode s positioned subcutaneously in direct contact with the person's blood stream.

Such mask and etching techniques are time consuming and costly. Because body fluids tend to degrade the electrode materials and proteins tend to deposit on the electrodes, the sensors have a relatively short life. For diabetics and others who monitor glucose or other body chemicals frequently and for extended periods it is therefore desirable to have an inexpensive sensor which is disposable at intervals of a few days.

For measurement of glucose levels, sensors typically employ an oxidase enzyme, particularly glucose oxidase. The oxidase acts on a substrate or analyte, such as glucose, to produce hydrogen peroxide, and in the process, oxygen is consumed. The concentration of glucose can be determined indirectly, such as by detecting the depletion of oxygen or the generation of reaction products, such as hydrogen peroxide or gluconic acid. U.S. Patent No. 4,970,145 discloses electrodes formed from platinized carbon particles on which an enzyme, such as glucose oxidase, is immobilized. U.S. Patent No. 5,160,416 discloses similar electrodes in which a mixture of the enzyme with finely divided platinum group metal or oxide particles and carbon powder in a suitable binder is deposited on an electrically conductive support material, such as carbon paper or a platinum strip. Both patents disclose the use of amperometric techniques to determine glucose levels.

The present invention provides a new and improved sensor and method of use which overcomes the above-referenced problems and others.

Summary of the Invention

A sensor system formed by printing electrodes on a support has a variety of applications for the detection of glucose and other chemicals in vivo and in vitro.

One advantage of the present invention is that a disposable sensor is readily formed.

Another advantage is that the sensor may be formed on a wall of a catheter.

Still further advantages of the present invention will become apparent to those of ordinary skill in the art upon reading and understanding the following detailed description of the preferred embodiments.

Brief Description of the Drawings

The invention may take form in various components and arrangements of components, and in various steps and arrangements of steps. The drawings are only for purposes of illustrating a preferred embodiment and are not to be construed as limiting the invention.

FIGURE 1 is a top view of a sensor according to the present invention;

FIGURE 2 is a perspective sectional view in partial section through A-A of the sensor of FIGURE 1;

FIGURE 3 is a schematic view of a combination infusion pump and glucose meter according to the present invention;

FIGURE 4 is a schematic sectional view of a sensor inserted through the wall of a catheter;

FIGURE 5 shows a sensor in use in a closed loop system;

FIGURE 6 is a schematic sectional view of a subcutaneous sensor system mounted to an exterior of a catheter wall and signaling a glucose meter, according to the present invention;

FIGURE 7 is a schematic sectional view of a subcutaneous sensor mounted to an interior of a catheter

wall and signaling a glucose meter coupled to an insulin pump;

FIGURE 8 is a top view of a sheet of support material with sensors printed thereon;

FIGURE 9 is a side perspective view of the support sheet of FIGURE 8 rolled into a catheter shape with the sensors on the exterior; and

FIGURE 10 is a side sectional view of an infusion set with a catheter passing through a person's skin.

Detailed Description of the Preferred Embodiments

With reference to FIGURES 1 and 2, a sensor **10** is shown. While the sensor is described with reference to glucose detection, it will be appreciated that the sensor may also be used for detection of other electrochemically detectable chemicals.

The sensor comprises a support **12**, formed from an insulative material, such as a sheet of polyester, polycarbonate, or polyimide. The support defines a well **14** adjacent one end of its upper surface **16**. A sensing material **18** is deposited at the base and on the sides of the well. The sensing material **18** includes an oxidoreductase enzyme, such as glucose oxidase, with is capable of catalyzing the reaction of a substrate or analyte (e.g., glucose). In the case of glucose, the glucose oxidase enzyme acts on the glucose to produce hydrogen peroxide, the reaction consuming oxygen. Other suitable oxidoreductases include uricase, lactase oxidase, cholesterol oxidase, and other peroxide-producing enzymes. Combinations of enzymes may also be used, as well as combinations of non-oxidases and oxidases, the non-oxidase acting on a substrate of interest to produce an oxidizable substrate for the oxidase. One such combination is beta-galactosidase and glucose oxidase for the determination of lactose.

The sensing material **18** preferably also includes a platinum group metal or metal oxide in finely divided form, which is relatively homogeneously mixed with the

oxidase. Suitable platinum group metals and oxides thereof include platinum, ruthenium, rhodium, iridium, palladium, and their oxides, and combinations thereof. Ruthenium is a particularly preferred metal. The sensing material may further include a carbon-containing material, such as finely divided carbon or graphite powder. Such materials preferably have a relatively large surface area of about 10 m^3/gm or higher, most preferably, in the range of 200-600 m^3/g. Preferably, the platinum group metal or metal oxide has a particle size in the range of from about 1 nm to about 20 μm, most preferably, in the range of 1-4 μm.

A droplet or layer of an analyte-containing liquid or viscous fluid **20** to be analyzed for the substrate is added to the well. An electrode system **22** detects a product generated (e.g., hydrogen peroxide or gluconic acid) or a chemical consumed (e.g., oxygen). Hydrogen peroxide is a particularly preferred detectable substance. A variety of electrode systems may be employed for detection. FIGURES 1 and 2 show a 3-electrode system, with a working electrode **24**, reference electrode **26**, and a counter electrode **28**, laid down generally in parallel on the support surface so that at least a portion of each of the electrodes is in contact with the fluid **20**. However, other electrode systems may also be employed, such as a two electrode system employing working and reference electrodes.

The electrode system is in electrical contact with the analyte **20**. As shown in FIGURE 1, the electrodes take the form of strips, laid down on the support, with contact pads **30** at a proximal end of the support for electrically connecting the electrodes with electrochemical equipment (not shown). A variety of electrochemical measurement techniques may be employed with the electrode system, including amperometric and potentiometric techniques. For example, a voltage is periodically applied between the working and reference electrodes **24**, **26** and the current generated due to reduction of hydrogen peroxide measured between the working and counter electrodes.

The electrode system generates an electrical signal (current in the above embodiment) which is related to (directly proportional to, in the case of glucose and hydrogen peroxide) the concentration of the analyte substance to be detected (e.g., glucose). Using a look-up table, the electrochemical monitoring system compares the detected signal with calibrated concentration/signal data and produces an output indicative of the concentration of glucose or other substance present.

Various conductive materials may be used for forming the electrodes. In a preferred embodiment, the working electrode is formed from nickel or silver, the counter electrode is carbon, and the reference electrode is an Ag/AgCl electrode. Other materials or combinations of materials may also be used as is known in the art.

The electrodes may be formed by a variety of techniques, including lithography, printing, and the like. The electrode materials, e.g., ruthenium and glucose oxidase for the sensing material **18**, are mixed together and combined with a carrier liquid to form a suspension which is deposited on the support. In a preferred embodiment, the electrodes **24**, **26**, **28**, and also the sensing material **18** and contact pads **30** are printed on the support material, for example by inkjet, offset, laser, silk-screen, or gravure printing techniques. Both thin and thick film printing techniques may be used.

Inks are prepared by combining the materials for the electrodes or sensing material with a suitable carrier, such as a liquid or a material which flows at the temperature of printing. The inks are then printed on the support and dried or otherwise fixed. The inks can be laid down in a multi-step process, by printing a first material, which is allowed to dry, followed by a second material, and so forth, until all the materials are laid down. In the case of the sensing material, the enzyme, metal or metal oxide, and carbon powder may be mixed together with a carrier liquid to form an ink which is printed on the

support. Or, the enzyme, metal or metal oxide, and carbon powder may be separately laid down, each one in a separate ink formulation.

For example, a thick film process can be used to produce the sensor. In this process, a silk screen printing process is preferably used. The design of the sensor elements is first transferred onto a screen (which can be a metal mesh or polymer screen) by a photographic method. The selected metal or conductive electrode materials can be prepared or purchased commercially in ink or paste form. Placing the substrate, such as a polyimide or other film, in a thick film printing printer with the patterned screening over the polyimide film, the ink or paste can be applied onto the polyimide surface through the patterned screen using a controlled squeegee. The ink can then be dried by heat or UV curing.

The carrier liquid may be an aqueous or organic liquid or combination thereof and is preferably one which is readily removed from the electrode material or sensing material after printing, e.g., by evaporation, although leave-in carriers are also contemplated. In the case of the sensing material, the enzyme is generally sensitive to heat. The ink is therefore dried or otherwise fixed at a temperature which does not adversely affect the activity of the enzyme.

Preferably, multiple sensors are printed at one time by forming an array of sensors on a large sheet of the support material. The sheet is then cut to form the individual sensors.

In one embodiment, the sensor **10** is used outside the body to determine the glucose level in a droplet of blood or other body fluid. The droplet is withdrawn from the body and placed in the well. To aid in positioning the droplet in the well, a layer **34** of a wicking material is attached to the support surface **16** over the general area of the well. The droplet is applied to the wicking material and carried thereby into the well.

To measure the glucose concentration, the sensor is electrically connected with an electrochemical monitoring system, such as a glucose meter **40** (See FIGURE 3). The glucose meter both supplies the applied voltage (or current) and detects the current (or voltage) signal generated. It will be appreciated that the two functions of applying voltage/current and detecting the signal generated may be performed by separate components, although for convenience these are shown as a single unit, the glucose meter.

FIGURE 3 shows the glucose meter in a housing **42**, which also holds an infusion pump **44**, although separate glucose meters are also contemplated. After applying the droplet, the sensor **10** is inserted into a suitably shaped slot **46** in the housing, the slot having electrical connectors (not shown) which electrically connect the contact pads **30** with the glucose meter. The glucose meter determines the glucose concentration and signals a controller **50** (which may be integral with or separate from the glucose meter). The controller **50** calculates an appropriate response to the detected level by accessing look-up tables. In one embodiment, the controller may recommend that a dose of a medicament (e.g., a number of ml of insulin) be supplied to the person (e.g., from the infusion pump). Or, the controller may recommend that the person ingest carbohydrate. The recommended dose or other action step to be taken is displayed in human readable form, such as on a display screen **54**. The person may accept the recommended dose, for example by pressing keys on a keypad **56**, or may enter a different dose to be taken. The controller then instructs the infusion pump **44** to deliver to the selected dose, for example, by operating a motor **58** to drive a piston **60** of a syringe **66** containing the medicament. The medicament, e.g., insulin, is carried by suitable tubing **68** from the syringe into the person's body.

In an alternate embodiment, the controller may override the person in selecting a suitable dose, so that the person is not injected with a dangerous level of the

medicament. In yet another embodiment, the personal input 56 is eliminated and the controller instructs the insulin pump directly.

In another embodiment, the sensor 10 is used to detect glucose or other body chemical a body fluid flowing through tubing, such as a catheter 70 (see FIGURE 4). For this embodiment, the support 12 is formed from a material (e.g., polyimide or polyurethane) and/or is shaped (e.g., with a rounded end 72 or pointed tip) so that it is capable of piercing the catheter wall 74. In this embodiment, the sensor support 12 is preferably formed from a rigid material and of a sufficient thickness that does not readily break during piercing. Catheters, in general, are formed from a relatively soft material, which is capable of being pierced. The electrode system 22 is thereby positioned to be immersed in the body fluid or other liquid to be analyzed in the bore 76 of the catheter. In this embodiment, the well 14 and wicking membrane 34 may be eliminated as the electrodes 24,26,28 and sensor material 18 are in direct contact with the analyte. The wicking membrane may be replaced with a protein-impermeable membrane or coating 80 or other membrane which inhibits the passage of materials which may be detrimental to the operation of the sensor. The membrane covers those portions of the sensor which are affected by the detrimental materials, such as the electrodes and/or the sensing material. The membrane 80 is, however, permeable to at least glucose (or other chemical to be detected).

Suitable protein impermeable membranes may be formed from a mixture of 2-hydroxyethyl methacrylate (HEMA), N,N-dimethyl amino ethyl methacrylate (DMAEMA) and methacrylic acid (MA), although other protein-impermeable materials are also contemplated. Alternatively or additionally, a coating which resists blood coagulation and protein binding may also be used, such as a mixture of polyethylene glycol (PEG) and heparin.

With reference to FIGURE 5, the sensor of FIGURE 4 may be employed in a loop system, such as a dialysis

system (see FIGURE 5). The loop system has one fluid path defined by a first catheter **84** which carries body fluid, such as blood, from a patient's body **86** to a dialysis machine **88** or other suitable monitoring or treatment equipment. A second, return catheter **90**, returns the treated body fluid back to the patient. The sensor **10** is inserted into one of the catheters **84, 90** (FIGURE 5 shows the sensor in the input line **84**), to detect the glucose content of the fluid flowing therethrough. The sensor may be operated continuously or intermittently, every few minutes, or as appropriate, to monitor the changing glucose level. The sensor is electrically connected by wiring **92** (or radio telemetry) to a glucose meter **94**, which may be housed with the dialysis machine. As before, the glucose meter uses electrochemical techniques to monitor glucose levels, for example, by directing the hydrogen peroxide generated by enzymatic conversion of the glucose in a small region of the body fluid adjacent the sensing element **18**. When the glucose meter registers that the glucose level is within a predetermined range, the glucose meter instructs the dialysis machine **88** to cease purifying the blood or to take other appropriate action. Alternatively, this operation may be conducted by a trained operator, who reads the glucose level detected by the glucose meter and programs the dialysis machine accordingly.

In another embodiment, shown in FIGURE 6, the sensor is employed for subcutaneous monitoring of glucose concentrations. The sensor **10** is mounted to a wall **100** of a catheter tube **102** such as a cannula, which may be employed to deliver insulin, or other medicament, to the persons blood or subcutaneous fluid. An infusion set **104** connected with a suitable insulin pump similar to that illustrated in FIGURE 3, or other delivery apparatus, delivers insulin to the catheter, which carries the insulin through the skin **106** and into a blood vessel, e.g., an artery, or into the interstitial fluid. The sensor may be positioned on an exterior surface **108** of the canula wall **100**, as shown in

FIGURE 6, or on an interior surface 110 of the wall, as shown in FIGURE 7. The sensor 10 generates an electrical signal in response to an applied voltage or current which is related to the glucose level in the blood vessel or interstitial fluid adjacent the sensor. Electrical wiring 112 (or radio telemetry) connects the sensor 10 with a glucose meter 114. As previously described, the glucose meter may be a separate unit (FIGURE 6) or housed together with an insulin pump 44 and controller 50 (see FIGURE 7), analogous to that shown in FIGURE 3.

When formed on the inside of the wall (FIGURE 7), the sensor 10 is used between dosages of insulin, when the catheter is filled primarily with interstitial fluid or blood and the fluid line 68 to the insulin pump 44 is preferably closed off.

The wiring 112 may be attached to the exterior 108 of the catheter wall 100 (FIGURE 6), attached to the interior surface 110, or integrally formed with the catheter wall 100 so that it is encased by the catheter wall (FIGURE 7).

In a preferred embodiment, illustrated in FIGURES 8 and 9, the electrodes 24, 26, 28 and sensing material 18 of the sensor 10, and optionally also a portion of the wiring 112 are applied directly to a surface 108, 110 of the catheter wall 100. The catheter wall 100 thus provides the support 12 for the sensor. The sensor may be formed, as shown in FIGURES 6 and 7, on an exterior or interior wall of the catheter, either by printing a preformed catheter or by forming the sensor components on a sheet 120 which is then rolled into the shape of the catheter and joined at a seam 122, either by welding or with a suitable adhesive.

The application of the sensor components 18, 24, 26, 28,30 is preferably achieved by printing the components on the sheet 120 or formed catheter, although other application methods are also contemplated. As shown in FIGURES 8 and 9, a number (two are shown) of sensors 10, 10' may be printed on a single catheter. As for the embodiment

of FIGURE 4, a protein impermeable membrane **80** is preferably formed over the sensor.

With reference now to FIGURE 10, the wiring **112** may be carried by the catheter **102** to a cannula housing **130** of the infusion set **104**. The infusion set comprises the cannula housing, which holds the upstream end of the catheter **102**, and an injection hub **132**, which carries a needle **136**. The injection hub is selectively linked to the cannula housing to supply insulin to the catheter via the needle **136**. The needle is fluidly connected with the fluid line **68** and carries the medicament through a septum **138**, mounted at the upstream end of the catheter, into the catheter bore.

The wiring **112** is connected to the glucose meter via a connection made when the hub **132** and cannula housing **130** are linked. Additional wiring **140** may be attached to the fluid line **68**, in a similar manner to wiring **112**, to electrically connect the wiring **112** with the glucose meter **114**, or radio telemetry may be used to transfer the signal thereto.

To use the sensor *in vivo* (i.e., transcutaneously), the cannula **102** with the sensor **10** formed thereon is inserted into the person's body with an insertion needle (not shown), for example, by replacing the injection hub **132** of the infusion set **104** with an insertion hub having a needle which extends through the cannula to just beyond the distal end of the cannula. The needle is inserted through the skin, carrying the cannula with it.

Once the cannula has been inserted, the insertion needle is withdrawn and the insertion hub replaced with the injection hub. The sensor is then ready for use. The sensor may be used continuously or intermittently to provide glucose measurements over a period of hours or several days. Typically, diabetics change the site of insulin injection every few days to prevent damage to the skin. With each change of site a fresh catheter is inserted into the skin, accompanied by a fresh sensor **10** or sensors. The sensor is

preferably configured (for example, with a protein-impermeable membrane) so that the signal does not degrade appreciably within the period of use, preferably functioning effectively for several days, or more.

As will be readily appreciated, the catheter with the sensor **10** printed thereon need not be used with an infusion set **104** as shown in FIGURES 6 and 7, but may be used with other methods of drug delivery, or may be used with a blood treatment system, such as the dialysis unit of FIGURE 5.

With reference once more to FIGURES 1 and 2, the sensor **10** may also include a heating element **150**, such as a resistance heater, which is formed on the support **12** in a similar manner to the other components (such as by printing). The element may be formed from platinum or other suitable metal. Electrical current is supplied to the heating element **150** via leads **152, 154**, which are also printed on the support **12**. The heater is used to maintain the analyte at an appropriate temperature for measuring glucose concentration (i.e., by changes in H_2O_2 or O_2 concentration). Since the rate of the enzyme catalyzed reaction between glucose and oxygen is dependent on the temperature of the analyte fluid, it is preferable for the sensor to operate at a predetermined selected temperature. In this way, the glucose meter does not have to access a calibration table which corrects for fluctuations in temperature. The heater can also be used as a temperature detector, detecting the temperature of the adjacent fluid by measuring the voltage across the resistance heater at a determined applied current. As will be appreciated, the heater may be formed on an opposite surface of the support to that carrying the electrodes **24,26,28** and sensing element **18** (except where the catheter is used as the sensor support).

The sensor may also be configured to measure other properties of the analyte solution, such as pH. FIGURE 1 shows a pH detector **160** formed on the surface **16** of the

support 12 (e.g., by printing). Additionally or alternatively, the sensor may be adapted to measure ketones, which can build up to dangerous levels, particularly in the blood of diabetics.

While the sensor is particularly applicable to detecting glucose in blood and other body fluids of humans, it may also be used in other animals and for detection of glucose and other analytes in non-body fluids.

The invention has been described with reference to the preferred embodiment. Obviously, modifications and alterations will occur to others upon reading and understanding the preceding detailed description. It is intended that the invention be construed as including all such modifications and alterations insofar as they come within the scope of the appended claims or the equivalents thereof.

Having thus described the preferred embodiment, the invention is now claimed to be:

1. A method of detecting an analyte in solution, the method including:

providing a sensor (10) for detecting the analyte on a fluid line (102);

inserting the fluid line in a person's body;

detecting a concentration of the analyte in body fluid surrounding the fluid line.

2. The method of claim 1, wherein the analyte includes glucose.

3. The method of claim 1, further including:

communicating the sensed analyte to an analyte delivery system; and

delivering a medicament to the person through the fluid line in accordance with the concentration of the sensed analyte.

4. The method of claim 3, wherein the analyte includes glucose and the medicament includes insulin.

5. The method of claim 1, wherein the sensor includes electrodes and/or other sensing elements (24, 26, 28, 18) which are printed on to a surface of the fluid line.

6. The method of claim 5, wherein the step of printing includes printing a sheet of material with a plurality of electrodes and/or other sensing elements;

sectioning the sheet into strips, each strip having a set of electrodes and/or other sensing elements for the sensor; and

forming each of the strips into a fluid line.

7. The method of claim 6, wherein each of the strips is printed with electrodes or other sensing elements (24, 26, 28, 18) for sensing at least two properties of the body fluid.

8. The method of claim 7, wherein the at least two properties are selected from the group consisting of glucose concentration, ketone concentration, and pH.

9. A sensor for detecting glucose or other analyte in solution the sensor including at least one electrode which is printed on an exterior surface of a fluid line, the fluid line being for delivering a medicament to a person, the sensor being capable of detecting the glucose or other analyte in the person's body fluid adjacent the fluid line when the fluid line is inserted into the person's body.

10. The sensor of claim 9, wherein the sensor includes a sensing material (18) which includes an oxidoreductase enzyme.

11. The sensor of claim 10, wherein the sensing material further includes:

a platinum group metal or metal oxide in finely divided form.

12. The sensor of claim 11, wherein the platinum group metal or metal oxide is selected from the group consisting of platinum, ruthenium, rhodium, iridium, palladium, and their oxides, and combinations thereof.

13. A sensing and injection system comprising:

a source of a medicament;

a pump for delivering the medicament to a fluid line, the fluid line having an end capable of being inserted into a person's body;

a sensor for an analyte positioned at or adjacent the end of the fluid line such that the sensor is capable of detecting the concentration of the analyte in the person's body fluid adjacent the end of the fluid line when inserted; and

a means for receiving the detected analyte concentration and determining an amount of medicament to be supplied in response to the detected analyte concentration.

14. The system of claim 13, further including:

a means for controlling the pump to deliver the determined amount of medicament.

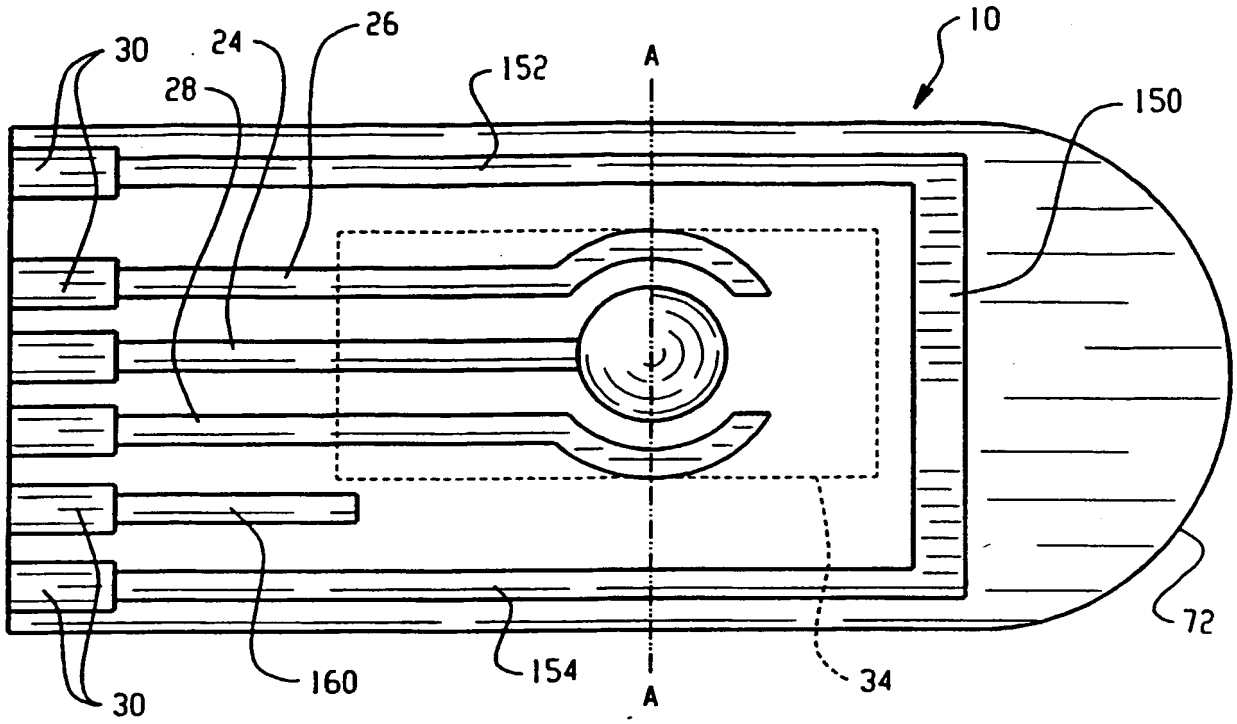

Fig. 1

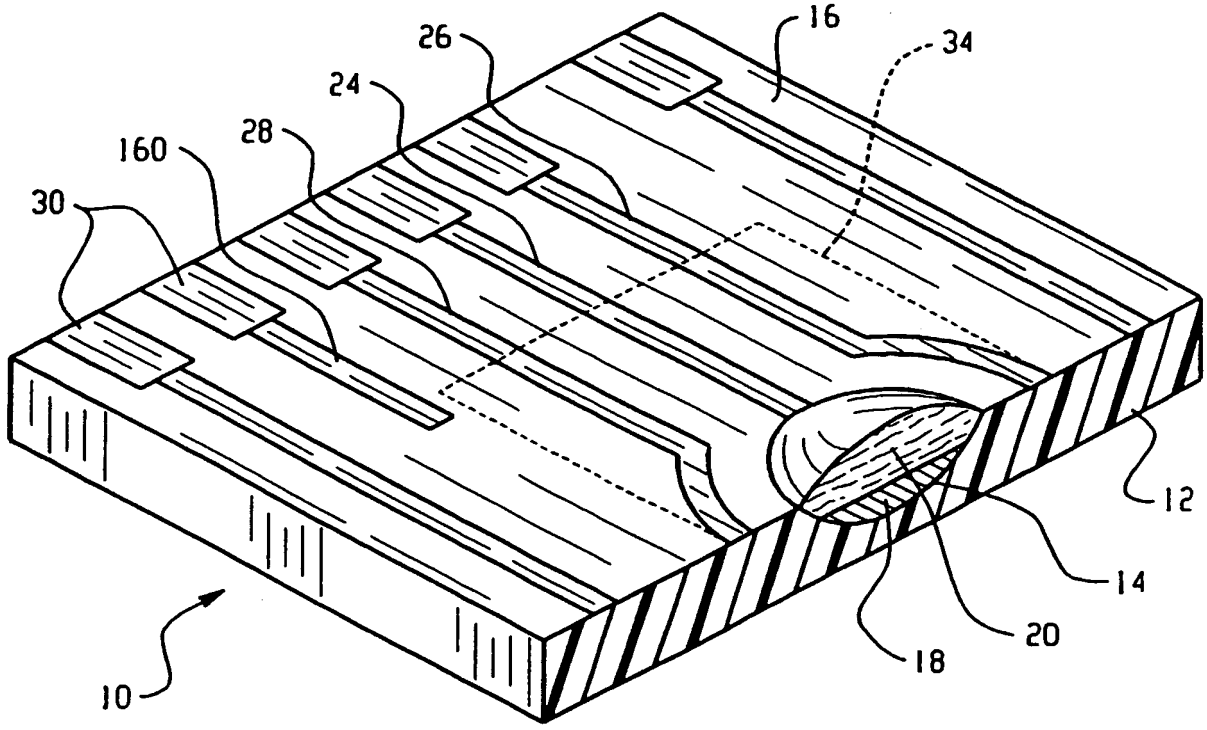

Fig. 2

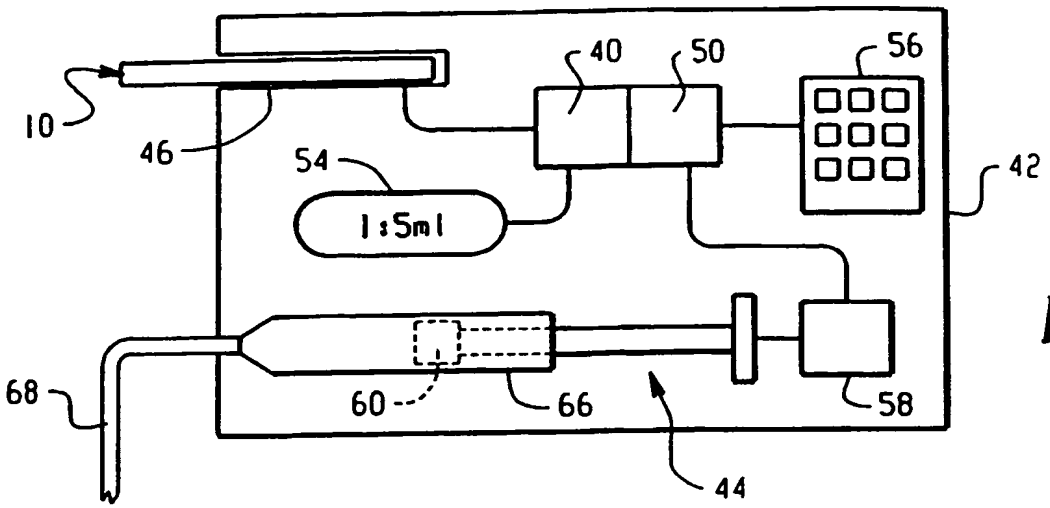

Fig. 3

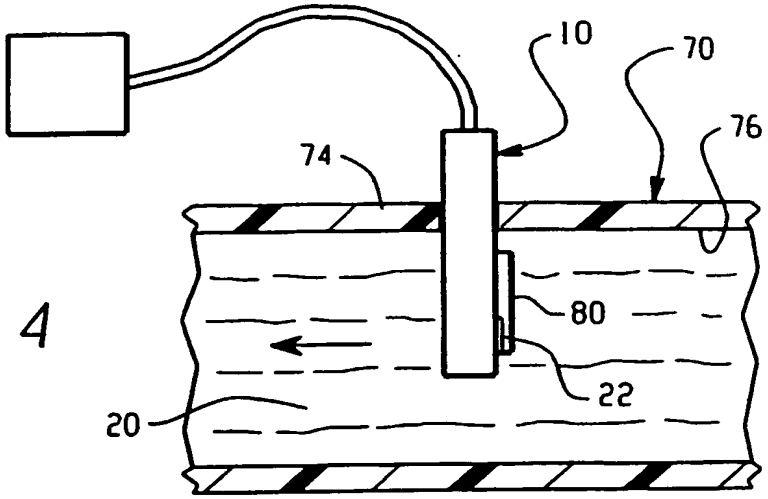

Fig. 4

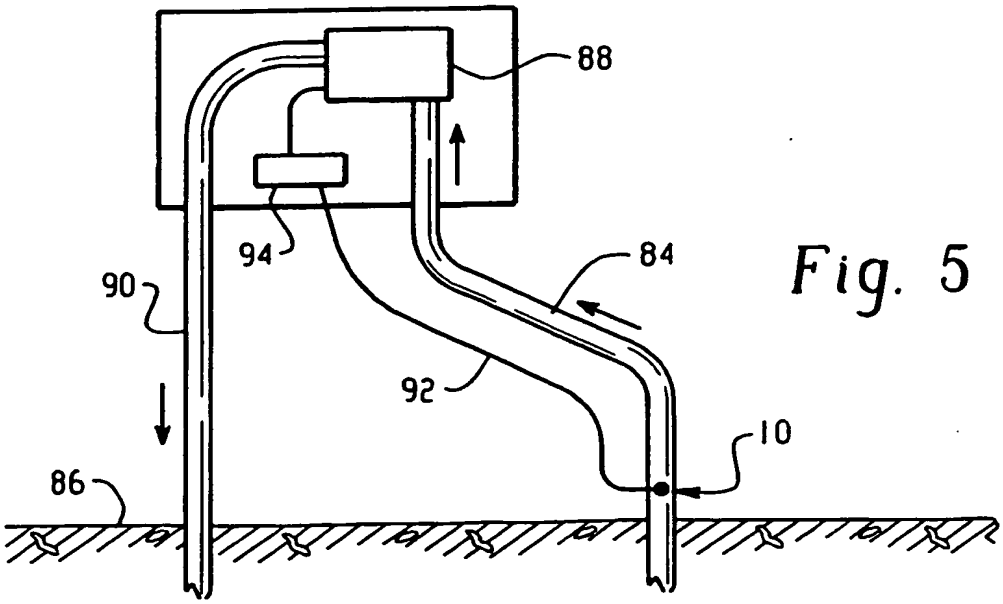

Fig. 5

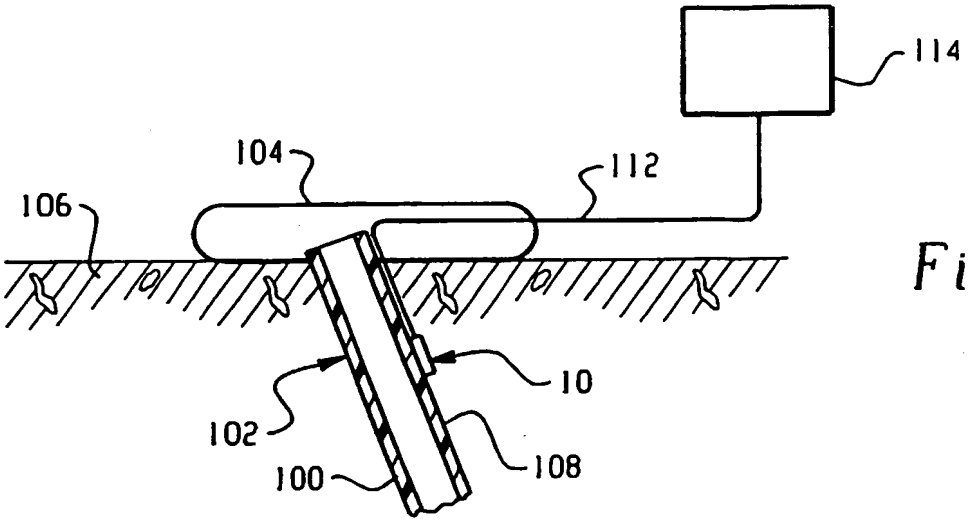

Fig. 6

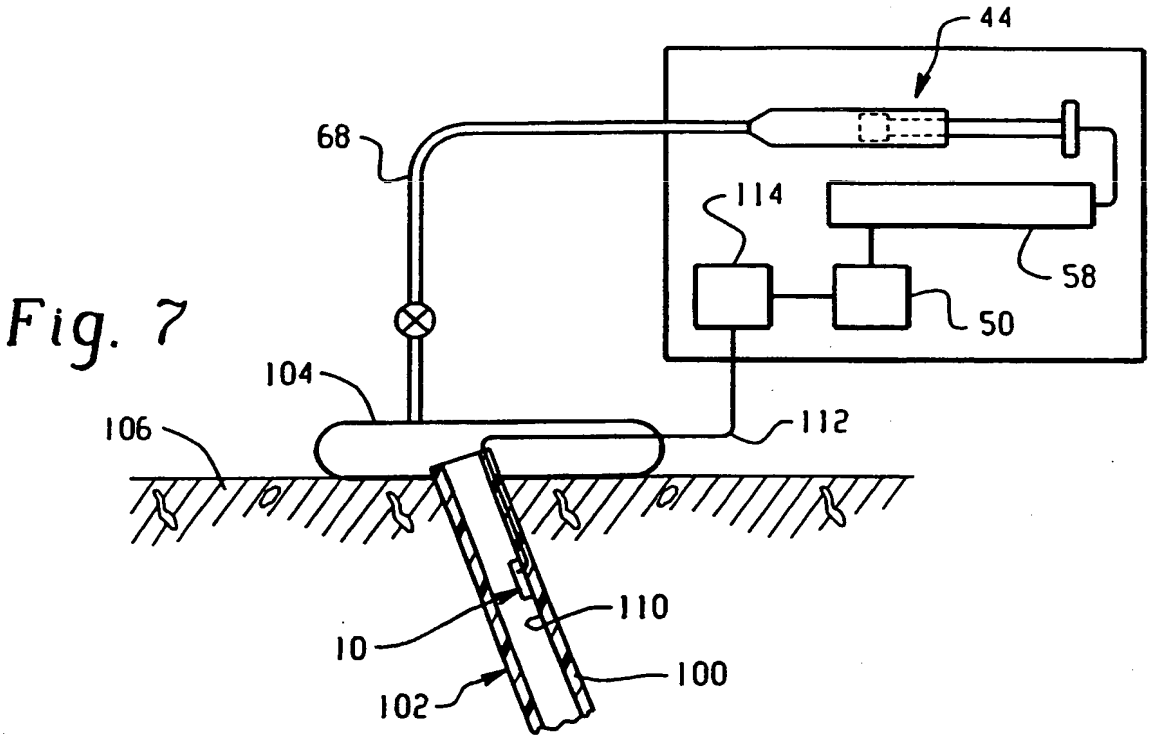

Fig. 7

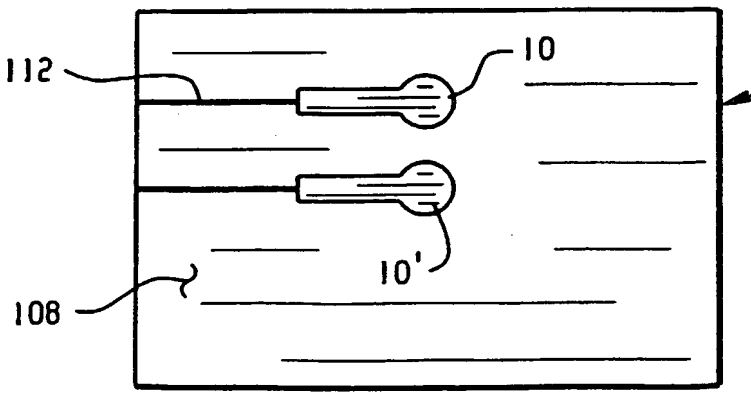

Fig. 8

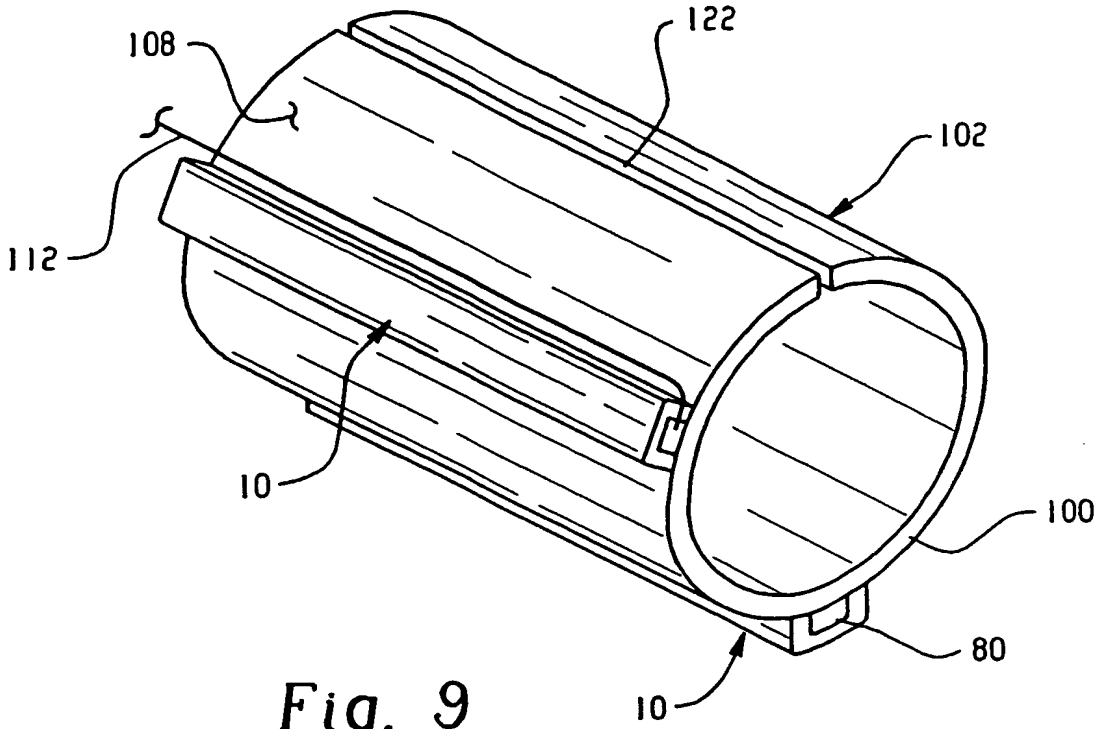

Fig. 9

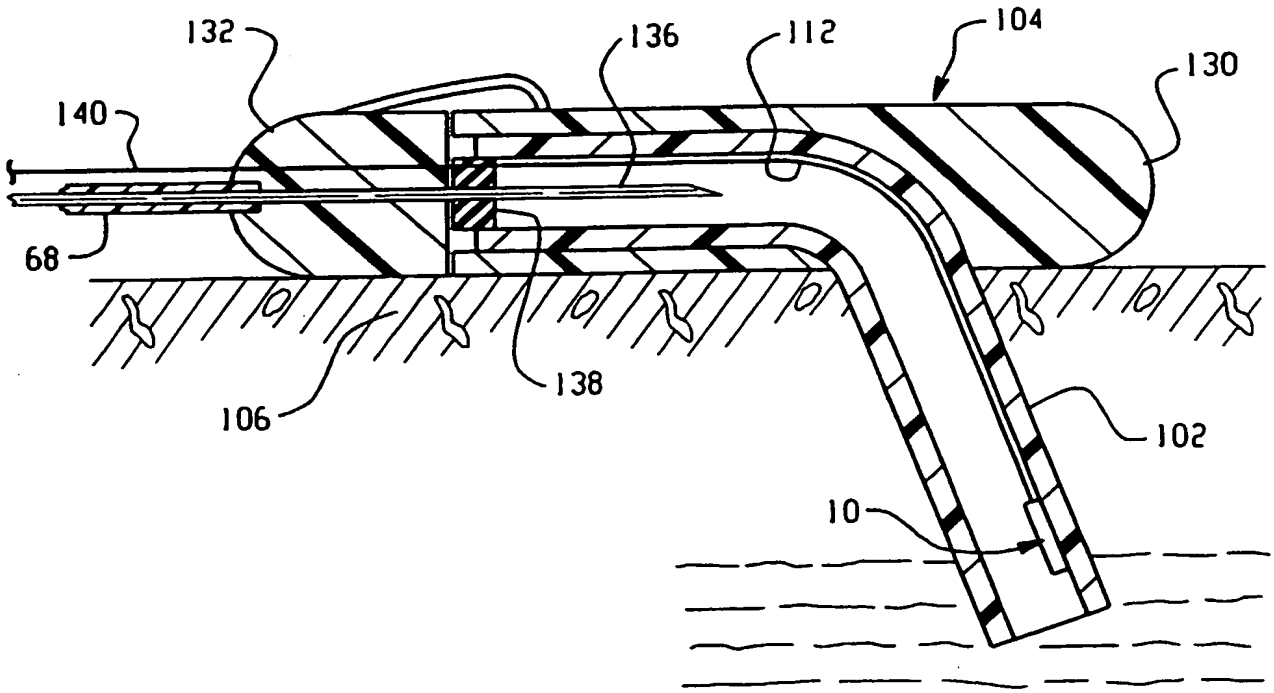

Fig. 10

INTERNATIONAL SEARCH REPORT

Interr I Application No
PCT/US 01/51213

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/00 A61M5/172

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 4 403 984 A (ASH STEPHEN R ET AL) 13 September 1983 (1983-09-13) column 14, line 43 -column 15, line 26 column 16, line 18 - line 45 figures 10,11,15,18	13,14 9-12
Y	US 5 497 772 A (LUCISANO JOSEPH Y ET AL) 12 March 1996 (1996-03-12) column 7, line 5 - line 11 column 8, line 14 -column 9, line 24	9-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 July 2002	06/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Martelli, L

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/51213

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-8
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr I Application No
PCT/US 01/51213

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